REMARKS

Upon entry of the present amendments, claims 25-30 and 36 will be pending in this application. Applicants have amended claims 25 and 30, and canceled withdrawn claims 1-24 and 32-34 without prejudice or disclaimer. No new matter has been added.

Sequence Rule Compliance

Applicants submit herewith a substitute Sequence Listing in computer readable form, a paper copy, and a statement under 37 C.F.R. § 1.821(f) to fulfill the requirements of 37 C.F.R. §§ 1.821-1.825. The amendments in the specification include inserting the paper copy of the Sequence Listing.

I hereby state that the content of the paper and computer-readable copies of the Sequence Listing, submitted in accordance with 37 C.F.R. §§ 1.821 (c) and (e), respectively, is the same and contains no new matter.

Applicants have also amended the specification as indicated herein to introduce sequence identifiers into the specification and to correct an obvious typographical error.

Withdrawn Rejections

Applicants thank the Examiner for withdrawing the written description and indefiniteness rejections of claims 25-30 and 36.

Rejections Under 35 U.S.C. §102

***Smith et al.* (Endocrine Reviews *18:621-645 (1997)*)**

The Office (at pages 5-6 of the Office Action) maintains its rejection of claims 25-30 and 36 as allegedly being anticipated by Smith et al. ("Smith"). Applicants respectfully disagree with the Office's position.

In part, the Office alleges, "Smith et al, throughout the publication, teach various compounds (peptidomimetics) that can be used for regulation of growth hormone (GH) secretion (see entire document)."

While it may be true that Smith describes compounds (peptidomimetics, i.e., agonists) that stimulate GH secretion, it does not describe the subject matter that is pending in the claims

(methods of identifying an *antagonist* of the GH/IGF-1 axis) and therefore does not anticipate the claims.

The amended claimed methods include the step of identifying a small molecule that is obtained by chemically modifying an agonist of a GH/IGF-1 axis activator[1] or that is selected for structural similarity to an agonist of a GH/IGF-1 axis activator *as an antagonist* of a GH/IGF-1 axis activator if the small molecule antagonizes the activity of the GH/IGF-1 axis activator.

Smith does not teach, or even suggest, this step. Rather, Smith describes the identification of growth hormone secretion agonists, i.e., compounds that have the opposite effect of the small molecules recited in the claimed methods.

At page 5 of the Office Action, the Office alleges, "The MK-0677 is a derivative of an antagonist or an agonist (p. 624, right col., para 2 and p. 625, left col., para 2), which reads on the chemically modifying an agonist of the GH/IGF-1 component of **clm 25**."

Applicants disagree with the Office's conclusion. MK-0677 was derived from a GH secretagogue (agonist), and MK-0677 itself functions as a GH secretagogue (agonist). MK-0677 does not function as an antagonist of a GH/IGF-1 axis activator. MK-0677 did not antagonize the activity of a GH/IGF-1 axis activator and was not identified as an antagonist of a GH/IGF-1 axis activator. Therefore, the cited text in Smith does not anticipate the methods of claim 25 or its dependencies.

The Office goes on to state at pages 5-6, "The reference also teaches particular dosing regimens of MK-0677 for dogs lowered IGF-1 to basal levels (p. 635, right col) and lowered GH levels to basal levels as well (p. 636, left col., para 1), which reads on the decreased levels of GH and/or IGF-1 of **clm 30**" (emphases in the original).

This is not true. Taking the cited passage from Smith in context, Smith merely discloses that levels of IGF-1 were allowed to return to basal levels. Smith does not indicate that MK-0677 *antagonizes* the GH/IGF-1 axis. Indeed, as Smith makes clear throughout its disclosure, MK-0677 is a GH secretagogue (agonist) (see, e.g., page 624, right column to page 625, right column; page 637, right column; Figure 4; Table 1).

In summary, Smith fails to teach, or even suggest, a method of identifying a GH/IGF-1 axis *antagonist*, not to mention a method that includes the steps recited in claim 25. For at least

[1] Solely to reduce the length of the description of a term in claim 25, in this response, the term "GHRH, GHRH-R, GHS, GHS-R, GH, GH-R, IGF-1, IGF-1R, PI(3) kinase, PDK-1, Akt-1, Akt-2, or Akt-3" has been abbreviated as "GH/IGF-1 axis activator".

these reasons, Applicants respectfully request that the § 102 rejection of claims 25-30 and 36 based on Smith be withdrawn.

Blum et al.* (Biochemistry *39:15705-15712 (2000)

The Office at page 7 of the Office Action alleges that claims 25, 26, and 36 are anticipated by Blum et al. ("Blum"). As part of its rejection, the Office alleges:

> Blum et al, throughout the publication teach using an inhibitor to inhibit IGF-1 receptor (Abstract). The reference teaches using various inhibitors such as I-OMe AG 538 for inhibition of IGF-R (e.g. p. 15707, right col. para 6; Table 1), and the chemical synthesis of the inhibitor (e.g., p. 15706, col. 1, para 3), which read on step a) of **clm 25**.

Applicants respectfully disagree with the Office's conclusions. Blum indicates that the I-OMe AG 538 inhibitor was designed based on the structure of another inhibitor, AG 538 (see, e.g., Blum Abstract).

In contrast, step a) of claim 25 recites providing a small molecule that is obtained by chemically modifying an agonist of a GH/IGF-1 axis activator or that is selected for structural similarity to an agonist of a GH/IGF-1 axis activator. Thus, Blum does not teach (or even suggest) this step of claim 25.

Further, Blum does not teach steps b) or c) of the claimed methods, which include evaluating activity of a GH/IGF-1 activator in the presence of the small molecule that is obtained by chemically modifying an agonist of a GH/IGF-1 axis activator or that is selected for structural similarity to an agonist of a GH/IGF-1 axis activator, and identifying the small molecule that is obtained by chemically modifying an agonist of a GH/IGF-1 axis activator or that is selected for structural similarity to an agonist of a GH/IGF-1 axis activator as an antagonist of a GH/IGF-1 axis activator if the small molecule antagonizes activity of the GH/IGF-1 axis activator.

For at least these reasons, Applicants respectfully request that the rejection of claims 25, 26, and 36 based on Blum be withdrawn.

Deghenghi (U.S. Pat. No. 5,962,409)

The Office (pages 7-8 of the Office Action) alleges that claims 25-27, 30, and 36 are anticipated by Deghenghi. The Office alleges:

> Deghenghi et al, throughout the publication, teach using peptides for inhibition of growth hormone (GH) secretion (Abstract). The reference teaches various peptides that inhibit the release of GH (e.g., cols. 1-2). The reference also teaches synthesis of cyclic

> peptides (e.g., col. 2, lines 1+; col. 3, lines 1+), which read on step a) of **clm 25**. (Office Action at page 7).

Applicants respectfully disagree with the Office's conclusions. Deghenghi describes the preparation of peptide inhibitors (antagonists) of growth hormone. These peptides are homologues of somatostatin (Deghenghi col. 1, lines 6-8). Somatostatin is an *inhibitor* of growth hormone (Deghenghi col. 1, lines 10-12). Somatostatin is not a GH/IGF-1 axis activator; rather, it is a GH/IGF-1 inhibitor. Thus, the peptides described by Deghenghi were designed based on the structure of a GH/IGF-1 axis *antagonist*.

In contrast, step a) of claim 25 recites providing a small molecule that is obtained by chemically modifying an agonist of a GH/IGF-1 axis activator or that is selected for structural similarity to an agonist of a GH/IGF-1 axis activator. Thus, because Deghenghi describes inhibitors prepared based on the structure of a GH/IGF-1 axis inhibitor, it does not teach (or even suggest) this step of claim 25.

Further, Deghenghi does not teach steps b) or c) of the claimed methods, which include evaluating activity of a GH/IGF-1 activator in the presence of the small molecule that is obtained by chemically modifying an agonist of a GH/IGF-1 axis activator or that is selected for structural similarity to an agonist of a GH/IGF-1 axis activator, and identifying the small molecule that is obtained by chemically modifying an agonist of a GH/IGF-1 axis activator or that is selected for structural similarity to an agonist of a GH/IGF-1 axis activator as an antagonist of a GH/IGF-1 axis activator if the small molecule antagonizes activity of the GH/IGF-1 axis activator.

For at least this reason, withdrawal of his rejection of claims 25-27, 30, and 36 is respectfully requested.

Orrego et al.* (J. Clin. Endocrinol Metab. *86:5485-5490 (2001))

The Office alleges that claims 25-30 and 36 are anticipated by Orrego et al. ("Orrego") (pages 8-9 of the Office Action). The Office alleges:

> Oreggo et al, throughout the publication, teach using an antagonist of GHRH-R to reduce GH in human (Abstract). The reference teaches administering a GHRH antagonist to human such as (N-Ac Tyr1, D-Arg2)GHRH-(1-29)-NH2) or GH-44, which compounds are modification of the GHRH (an "agonist"). (e.g. p.5486, col. 1, para 1; Figure 1; Figures 2-4). The GHRH antagonists read on the antagonist obtained from an agonist of **clm 25**, and the administering reads on the steps of **clm 25**.

Applicants respectfully disagree. Oreggo discloses that two different GHRH antagonists ((N-Ac-Tyr_1, D-Arg_2)GHRH-(1-29)-NH_2) and GH-44) were administered to patients, but it does not indicate how these antagonists were designed. Specifically, Oreggo does not teach antagonists that were obtained by chemically modifying an agonist of GHRH, or any other GH/IGF-1 axis activator, or that were selected for structural similarity to an agonist of GHRH, or another GH/IGF-1 axis activator. The passage on page 5486 that the Office cites merely identifies the commercial suppliers of the two antagonists and the doses that were administered.

In contrast, step a) of claim 25 recites providing a small molecule that is obtained by chemically modifying an agonist of a GH/IGF-1 axis activator or that is selected for structural similarity to an agonist of a GH/IGF-1 axis activator. Orrego fails to teach this step.

Further, Orrego fails to disclose evaluating activity of a GH/IGF-1 activator in the presence of a small molecule that is obtained by chemically modifying an agonist of a GH/IGF-1 axis activator or that is selected for structural similarity to an agonist of a GH/IGF-1 axis activator as an antagonist of a GH/IGF-1 axis activator, as recited in step b) of claim 25. Orrego also fails to describe identifying such a small molecule as an antagonist of a GH/IGF-1 axis activator if the small molecule antagonizes the activity of the GH/IGF-1 axis activator, as recited in step c) of claim 25.

Because Orrego fails to teach, or even suggest, any of the steps recited in claim 25, Applicants respectfully request that the rejection of claims 25-30 and 36 based on this reference be withdrawn.

CONCLUSION

For at least the reasons stated above, Applicants respectfully submit that all pending claims are in condition for allowance, which action is expeditiously requested. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

A Request for Continued Examination (RCE) and its associated fee are being submitted herewith.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. Please charge any deficiency to Deposit Account No. 50/2762.

Respectfully submitted,
Di Stefano et al., Applicant

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